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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/410,539	03/24/1995	MATTHEW B. WHEELER	7823/5	2654

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EXAMINER	
CROUCH, DEBORAH	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 06/29/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/410,539	WHEELER, MATTHEW B.	
	Examiner	Art Unit	
	Deborah Crouch, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 April 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,9-12,14-20 and 22-77* is/are pending in the application.

4a) Of the above claim(s) *14-20 and 22-77* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6 and 9-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The Examiner of record has now changed. The Examiner is now Deborah Crouch of Art Unit 1632.

Applicant's arguments filed April 15, 2004 have been fully considered but they are not persuasive.

Claims 1-6, 9-12, 14-20 and 22-77 are currently pending. Claims 14-20 and 22-77 are withdrawn from consideration; claims 14 and 22-77 are directed to non-elected claims. Claims 1-6 and 9-12 are under current examination.

The declaration by Dr. Nick Strelchenko has been received, but is not found persuasive for reasons presented below.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

The prior rejection of claims 1-6 and 9-12 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6, 9-12 of U.S. Patent No. 5,942,435 [formerly U.S. Application No. 08/473,030] is maintained for reasons presented in the office action mailed June 17, 2003.

Applicant reiterates that they will file a terminal disclaimer once allowable subject matter is indicated.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 3 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement for reasons present in the office action mailed June 17, 2003. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claim is directed to methods of making a chimeric ungulate comprising the introduction of a totipotent ungulate embryonic stem cell that has a first genetic complement into a recipient embryo of the same species as the embryonic stem cell, said recipient having a second genetic complement, to form a chimeric ungulate embryo, and placing the chimeric ungulate embryo in an environment suitable for the complement of development to form a chimeric ungulate.

The enablement rejection pertains to the predictability of producing or obtaining totipotent embryonic stem cells.

Applicant argues that the Board agreed that germ line transmission of embryonic stem cells to produce chimeric ungulates was not required, and thus the argument about totipotency is not relevant for claims 1-6 and 9-12. Applicant argued that totipotent cells and transgenic animals are preferred but not required.

The issue is not whether or not there was germ line transmission in the chimeric ungulates. Applicant has misread the rejection. The previous office action, mailed June 17, 2003, states the rejection pertains to "the predictability of producing or obtaining totipotent embryonic stem cells." Thus, the skilled artisan at the time of filing could not have implemented claim 3 because totipotent ungulate ES cells were not available at the time of filing. Each element of a claim must be enabled, that is available to the public. As the rejection clearly states, this was not the case for totipotent ungulate stem cells. The previous office action presents this argument complete with art references to support the rejection.

Applicant argues that the Board never said totipotent cells were not enabled. Applicant argues that the Board did not dispute enablement isolating porcine ES cells, where the rejection was to the breadth including all ungulates. Applicant argues that "pluripotent or totipotent" is not the basis of the Board's affirmance of the rejection of claims 15-20. These arguments are not persuasive.

Apparently the Board stated that the specification defined ES cells as including totipotent, and then continued on to discuss the specification to be enabling for pluripotent ES cells. There is no statement that the cells are totipotent. On the issue of totipotency of the cells, the Board is silent. However, the issue is that claim 3 requires the cells to be totipotent. It is the making and obtaining of totipotent ES cells for use in implementing claim 3 that is not enabled. The Board never said that totipotent ES cells were enabled. Further, any attempt by applicant to state that totipotent cells are not a required element for claim 3 is an error.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 4, 5 and 10 remain rejected under 35 U.S.C. 102(b) as being anticipated by Evans *et al.* [WO 90/03432, published 5 April 1990, cited in Applicants' Information Disclosure Statement, filed 6/4/1996, Paper No. 10] for reasons presented in the office action mailed June 17, 2003.

Evans teaches methods of producing pluripotent ES cells from ungulates, such as porcine and bovine species. See *Abstract*. Evans discusses the methods for introducing genetic alterations into a mammal, which can lead somatic genetic mosaicism. See p. 4, 2nd ¶. Particularly, Evans teaches the isolation of pluripotent ES cells from ungulate embryos [bovine and porcine]. See pp. 8-11.

Note that the specification defines a *genetic complement* as, "[A]ll genes present, or may designate a particular gene or genes of interest. Therefore, a complement may be "different" because it has a different allele of a gene, or a different gene or genes and may be from a different species." See pp. 11-12, bridging ¶. As such, in view of the teachings of the specification, the surrogate mother would have a different genetic complement than that of the blastocyst, as they would be expected to have different alleles of a gene, for example.

Applicant has provided a declaration by Nick Strelchenko stating the cells described in Evans are not ES cells. Declarant makes this determination on morphological differences between the ES cells of Evans, exemplified by mouse cells, and the porcine ES cells of Wheeler. While there is no mistake in the finding that the exemplified mouse ES cells of

Evans appear different from the porcine ES cells of Wheeler, there is no evidence that the porcine ES cells disclosed by Evans would be pluripotent and contribute to the chimerism disclosed also by Evans. Declarant is not persuasive because there is no evidence of record that morphological differences alone enable the determination of whether an ES cell is pluripotent. At pages 19-20, Evans describes the isolation of porcine ES cells. Applicant has not provided an evidence that these porcine cells would not be pluripotent, which applicant has stated on this record are all that are needed for the invention. Furthermore, at page 11, Evans states that the observations disclosed demonstration that the cell cultures described are "indeed embryonic stem cells."

Applicant argues that the ES cells of Evans are different from those of Wheeler as disclosed in the present specification. Applicant argues that ES cells are defined based on morphology under certain conditions and the cell type being defined at a stage of development and being predicative of totipotency. Applicant argues that the ES cells of Evans are not shown to produce tumors capable of differentiating into multiple cell types. Applicant argues that the morphology of the cells of Evans is not consistent with the morphology of the ES cells presently disclosed. These arguments are not persuasive.

The issue is not whether or not the ES cells of Evans look like applicant's cells. Evans says they are ES cells, and thus they remain so defined until proven otherwise. Applicant has not provided any evidence, such as their mention of tumor formation in vivo comprising the three germ layers, that the ES cells of Evans would not so form tumors. As stated in the rebuttal to the statements by declarant Strelchenko above, there is no evidence of record that a difference in morphology alone means that the ES cells of Evans are not ES cell. Additionally,

Claim Rejections - 35 USC § 102/103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 2, 4, 5 and 6 remain rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Kashiwazaki *et al.* [**The Veterinary Record**, 130(9):186-187 (1992), for reasons presented in the office action mailed June 17, 2003.

Kashiwazaki teach methods of producing chimeric pigs. They teach that blastocysts produced from the mating of Large White cross Large White, or Landrace cross Large White pigs [white in coat color] were used as the donor embryos. See p. 186, 2nd column, 2nd ¶ of the reference. Host blastocysts, which were brown in coat color, were collected from Duroc females. Dissociated inner cell mass cells were introduced into the blastoceole of the donor blastocysts. The resulting embryos were then transferred to recipient gilts, and two of the three recipients became pregnant and delivered a total of 11 piglets. One offspring was chimeric, and another had a complete white coat color, indicating a large contribution from the injected inner cell mass cells. It was found that the porcine inner cell mass cells could contribute efficiently to the development of pigs when injected into blastocysts. See p. 187, 1st ¶.

Applicant argues that this rejection was overcome by insertion of the word "cultured" to modify ES cell. This is not persuasive.

None of claim 1, 2 and 4-6 contains the word "cultured." Further, Kashiwazaki states that donor blastocysts were cultured, so inherently the inner cell mass cells, from which ES cells are derived, were cultured. Kashiwazaki also states that isolated inner cell mass cells were dissociated by incubation in phosphate-free buffer. Thus, Kashiwazaki clearly teaches the inner cell mass or ES cells were cultured.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 9-12 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Evans et al. [WO 90/03432, published 5 April 1990] when taken with Clark *et al.* [**Genome** 31(2):950-955 (1989)] for reason presented in the office action mailed June 17, 2003. Evans teaches methods of producing pluripotent ES cells from ungulates, such as porcine and bovine species. See *Abstract*. Evans discusses the methods for introducing genetic alterations into a mammal, which can lead somatic genetic mosaicism. See p. 4, 2nd ¶. Particularly, Evans teaches the isolation of pluripotent ES cells from ungulate embryos [bovine and porcine]. See pp. 8-11. They further discuss utilizing the ES cells for the production of embryos carrying particular genetic backgrounds or specific mutations. See p. 11, 4th ¶. They further teach that prior to introduction to the host blastocyst, the ES cells can be genetically manipulated to express a gene of interest, "It can allow the use of stem

cells genetically transformed in such a way as to introduce a novel protein production in a specific part (*e.g.*, the mammary gland, the liver) of a subsequently derived chimæric animal." See p. 12, 1st full ¶.

Clark *et al.* [**Genome** 31(2):950-955 (1989)] teach methods of targeting expression of DNA sequences of interest to the mammary gland. They particularly teach the construction of a fusion gene comprising beta-lactoglobulin sequences and sequences encoding human factor IX. See p. 952, 2nd column, *Fusion constructs*.

Applicant argues that Clark teaches the production of transgenic animals, not chimeric animals. Applicant argues that the Board of Appeals agreed that transgenic animals and chimeric animals are completely different categories of animals. Applicant argues that Clark microinjected the DNA construct encoding Factor IX into a fertilized egg. Applicant argues that Clark states that the only route for gene transfer in domestic livestock was by pronuclear injection. These arguments are not persuasive.

Clark was cited to modify Evans which states that the ES cells described therein can be used to produce chimeric animals that express a gene of interest. Clark was used to provide teachings and motivation for producing an animal expressing a gene of interest.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until

after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deborah Crouch, Ph.D. whose telephone number is 571-272-0727. The examiner can normally be reached on M-Th, 8:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on 571-272-0408. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Deborah Crouch

Deborah Crouch, Ph.D.
Primary Examiner
Art Unit 1632

June 25, 2004